UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,744	10/30/2003	Patrizia Paterlini-Brechot	2121-0178P	7652

2292 7590 06/28/2006

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,744	PATERLINI-BRECHOT, PATRIZIA	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,9-18 and 20-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,9-18 and 20-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed March 31, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. In particular, the rejections under 35 U.S.C. 102 and 103 over Vona et al are withdrawn in view of the filing of a certified translation of the foreign priority document, which establishes the date of priority of the present invention to April 30, 2001.

Claims 1, 4, 5, 9-18, and 20-29 are pending and have been examined herein.

This action is made final.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 9-12, 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (American Journal of Pathology. January 2000. 156: 57-63; cited in the IDS).

Kalionis teaches a method for prenatal diagnosis of fetal cells isolated from maternal blood. The reference (page 3) states that "(t)he present invention is directed to a method for easily enriching and identifying trophoblast cells in maternal peripheral blood in the presence of a population of blood cell types. The enrichment, identification and analysis of trophoblast cells in peripheral blood provides a means by which non-

invasive prenatal diagnosis can be carried out. This method is therefore of particular value in prenatal testing to obtain genetic and/or biochemical information about the fetus."

The method of Kalionis (pages 5-7) comprises the steps of:

a) filtering a sample of maternal blood through a filter according to size, in order to separate fetal cells from maternal blood cells;

b) analyzing the cells retained on the filter by immunostaining for trophoblast-specific markers, in order to confirm the identify of the cells as being of fetal origin (see also page 8);

c) analyzing individual cells by in situ hybridization and immunostaining to demonstrate that the cells are fetal cells (see also pages 10 and 18); and

d) analyzing the individual fetal cells to detect a genetic anomaly or to determine the sex of the fetal cells (see also pages 9-10 and page 21).

Kalionis does not teach collecting individual fetal cells by microdissection, wherein the microdissection uses a laser to recover single collected cells in a tube.

However, Vona teaches methods for isolating rare cells from blood wherein the methods comprise passing a blood sample through a filter to retain target cells according to size, analyzing the cells retained on the filter to confirm their identity, using microdissection with the aid of a laser to individually collect the isolated cells retained on the filter into a tube in order to obtain a single collected cell (see pages 58-60). Vona (page 60) teaches that the isolated cells are then lysed and preamplified by PCR prior to genetic analysis using less than one fifth (i.e., 5 out of 60 ul) of the preamplified DNA

preparation. It is stated that the use of microdissection to isolate individual cells, followed by the amplified of DNA from the individual cells provides the advantage of a highly sensitive technique for detecting genetic abnormalities (page 58). It is also stated that the method of isolating cells by filtration followed by amplification of the nucleic acids in the isolated cells provided improved results over methods which relied on PCR alone (pages 58 and 62). The method is characterized as being "easy to perform, rapid, and inexpensive" (page 61). The method also provides the advantage of allowing for the isolation of individual cells without damaging the morphology of the cells, thereby providing increased sensitivity (page 61). Additionally, Vona (page 62) states that the method "allows the isolation of large, circulating, nontumorous cells. For example, the isolation of trophoblastic cells from the peripheral blood of pregnant women has been initiated in our laboratory and may constitute an important step toward improving the prenatal diagnosis of genetic diseases."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have individually collected the fetal cells by laser microdissection as disclosed by Vona in order to have provided an efficient and effective means for obtaining the individual fetal cells that would allow for the confirmation of the identity of the individual cells and the genetic analysis of the individual cells. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have preamplified the genetic material obtained from the isolated cells in order to have achieved the benefit

set forth by Vona of increasing the sensitivity of detection of genetic anomalies in the isolated cells.

With respect to claim 20, the reference teaches that the maternal blood samples are obtained form women at 30-37 weeks of pregnancy (see Table 1).

With respect to claim 21, the reference (page 7) teaches obtaining and filtering 5-100 ml of maternal blood.

With respect to claim 22, Kalionis teaches that the blood can be diluted with an isotonic buffer to reduce the viscosity prior to filtering. Kalionis does not exemplify diluting the blood 10 to 100 fold. However, Vona (page 58) teaches collecting 6 ml of blood and diluting the blood 1:10 in filtration solution prior to filtering. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have diluted the blood 1:10 fold in filtration solution prior to filtering in order to have reduced the viscosity of the blood and thereby to have optimized the filtration process and the isolation of individual fetal cells for prenatal diagnosis.

With respect to claims 23-25, Kalionis does not teach filtering the blood sample through a polycarbonate membrane with a pore density is in the range of "5 X 10^4 to 5 X 10^5 pores/m^2" (or 5 X 10^4 to 5 X 10^5 pores/cm^2) and does not specifically teach pore sizes of 8 um. However, regarding claim 23, Kalionis does teaches that the filter has a pore size of 10 um (page 4), which is considered to meet the limitation in the claim of "about 8 um." Further, Vona (page 58) teaches that the blood samples are filtered through a polycarbonate filter calibrated with 8um cylindrical pores. Vona also teaches

that each sample is filtered through a 0.6-cm diameter circular spot on the filter and that the cells were laser cut from the filter for collection. To have determined the optimum density of the pores that would have allowed for the isolation and collection of individual fetal cells would have been obvious to one of ordinary skill in the art and well within the skill of the art. As discussed in MPEP2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In particular, Vona teaches the criticality of selecting an appropriate filter wherein the filter and pore sizes are sufficient to retain the cell of interest and wherein the pores are spaced sufficiently a part to allow for the separation and collection of individual cells. Accordingly, the selection of a polycarbonate filter having an optimum pore density, including a pore density of 5×10^4 to 5×10^5 pores/cm^2 , would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made in order to have to have accomplished the objective of isolating and collecting the single fetal cells, thereby facilitating the method of prenatal diagnosis.

RESPONSE TO ARGUMENTS:

In the response, Applicants traverse this rejection by arguing that Kalionis does not teach or suggest isolation isolation and lysis of an individual cell. This argument has been fully considered but is not persuasive because Kalionis was not cited for this teaching. Rather, Vona was cited for teaching that methodology of isolating and lysing individual cells, amplifying the genome of an individual cell and analyzing the nucleic

acids of the amplified genome. There is no requirement for Kalionis to provide such teachings since the present grounds of rejection are made under 35 USC 103 and not under 35 USC 102.

Applicants assert that Vona teaches that ISET may have the potential use for isolating trophoblastic cells from peripheral blood of pregnant women, but that these teachings are only hypothetical. It is asserted that because the reference states that "further studies (...) have to be performed to define the size threshold of ISET application," Vona has not enabled the application of ISET to prenatal diagnosis.

These arguments have also been fully considered but are not persuasive because there is no requirement for Vona to demonstrate the successful application of the ISET method to fetal cells. Again, the present rejection is made under 35 USC 103, not under 35 USC 102 and there is no requirement for either of the cited references to demonstrate completion of the claimed invention. Rather, the standard for obviousness is whether the combined references when taken collectively would have both suggested the claimed invention and provided a reasonable expectation of success. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). In the present situation, the teachings of Vona provide both the motivation to combine teachings and a reasonable expectation of success. In particular Vona specifically states that "(t)he potential uses for ISET go well beyond the field of oncology, because it also allows the isolation of large, circulating, nontumorous cells. For example, the isolation of trophoblastic cells from the peripheral blood of pregnant women has been initiated in our laboratory and may constitute an important step toward improving the prenatal diagnosis of genetic

diseases." Further, Applicant's response does not provide any specific arguments as to why the method of Vona is not enabling. That is, there are no specific arguments provided as to why one of ordinary skill in the art, apprised of the ISET methodology and the teachings of Vona to use this methodology to isolate trophoblast cells from pregnant women and use the resulting isolated cells for prenatal diagnosis, would not be able to successfully practice such a methodology.

Applicants argue that Vona does not teach each of the elements of the claimed invention, including steps of analyzing filtered cells, pre-amplifying the genome of an isoaltd cell, using the pre-amplified genome to demonstrate the fetal origin of a cell and carry out prenatal diagnosis of cells demonstrated to be of fetal origin. These arguments are also not persuasive because applicants are arguing the references separately. Such arguments are entitled to little weight, where, as here, the rejection is based upon the combined disclosure of the references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The test of obviousness under 35 U.S.C. 103 is not express suggestion of the claimed invention in any or all of the references but what references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them (In re Rosselet, 146 USPQ 183(CCPA 1965).

3. Claims 13, 14, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000) and further in view of Bianchi (U.S. Patent No. 5,614,628; cited in the IDS) .

The teachings of Kalionis and Vona are presented above.

With respect to claim 13, the combined references do not teach sequencing the amplified fetal DNA. However, Bianchi (paragraph 31) teaches sequencing amplified fetal DNA in order to detect the presence of genetic variation in the fetal DNA and

teaches that sequencing may be used in place of or in addition to detection of genetic variations by PCR or hybridization analysis. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have sequenced the amplified fetal DNA in order to have achieved the benefit of providing a sensitive and effective means for detecting genetic variation in the fetal DNA thereby facilitating the method of prenatal diagnosis.

With respect to claim 14, the combined references do not teach using a probe to analyze the amplified DNA. However, Bianchi (e.g., paragraph 31) teaches that PCR amplified DNA can be analyzed by probe hybridization to detect nucleic acid sequence variations. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have detected the amplified fetal DNA by probe hybridization in order to have achieved the benefit of providing a sensitive and effective means for detecting genetic variation in the fetal DNA, thereby facilitating the method of prenatal diagnosis.

With respect to claim 16, Kalionis does not specifically teach detecting at least one polymorphism, such a SNP. However, Bianchi teaches methods of prenatal diagnosis which include the detection of polymorphisms, such as that associated with sickle cell anemia (see paragraph 46) and paternally inherited polymorphisms (paragraph 35). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have specifically detected a polymorphism associated with sickle cell anemia in order to have allowed for the prenatal diagnosis of sickle cell anemia or to have specifically

detected the paternally inherited polymorphism disclosed by Bianchi in order to have confirmed the identity of female fetal cells and to have distinguished female fetal cells from maternal cells.

With respect to claim 17, the combined references do not teach analyzing the fetal nucleic acids in order to demonstrate the biparental contribution of fetal DNA.

However, Bianchi teaches methods of prenatal diagnosis wherein the methods are carried out using nucleic acid probes that detect nucleic acids that are specific for both maternally and paternally derived nucleic acid sequences (see, e.g., paragraph 35 and 104-106). In view of the teachings of Bianchi, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have analyzed the fetal nucleic acids for markers specific for each parent in order to have provided a method that would have allowed one to distinguish between female fetal DNA and maternal DNA, thereby confirming the identity of the fetal cells and which would have allowed for the identification of both paternally and maternally inherited sequences in the fetal cells.

RESPONSE TO ARGUMENTS:

In the response, Applicants traverse this rejection by arguing that Bianchi teaches away from the claimed invention because Bianchi teaches the use of antibodies and flow cytometry to separate and isolate fetal cells.

This argument has been fully considered but is not persuasive because the teaching of an alternative method for isolating fetal cells is not equivalent to a "teaching

away." There is no disclosure in Bianchi which specifically indicates that the ISET method of Vona should not or could not be used to isolate and analyze fetal cells.

It is argued that Bianchi teaches the isolation of undifferentiated hematopoietic cells but does not teach the isolation of epithelial cells, such as trophoblast cells. This argument is not persuasive because Bianchi was not cited for its teachings of isolating epithelial cells. Rather, Bianchi was cited for its teachings of methods of prenatal diagnosis in which both maternal and paternal nucleic acids are analyzed, methods of sequencing of amplified nucleic acids, methods in which probes are used to analyze amplified nucleic acids and methods of prenatal diagnosis by detecting polymorphisms. Kalionis and Vona were each cited for their teachings of the analysis of trophoblast cells for the purposes of prenatal diagnosis.

4. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000) and Fodor (U.S. Patent No. 6,309,822) .

The teachings of Kalionis and Vona are presented above. The combined references do not teach detecting a genetic anomaly or genotype using DNA probes fixed to a microarray.

However, Fodor teaches methods for detecting mutations and polymorphisms using microarrays wherein a nucleic acid probe comprising a mutation/polymorphism or a wildtype sequence is immobilized onto an array and the array is contacted with a sample nucleic acid (see, e.g., paragraphs 714-716). Fodor (paragraph 368) states that microarrays can be used to simultaneously analyze multiple samples for a large number

of genetic markers and allows for simplified, economized and more generally accessible prenatal screening.

In view of the teachings of Fodor, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have detected the genetic mutations or polymorphisms using a microarray in order to have obtained the advantages set forth by Fodor of providing a method which allowed for the simultaneous analysis of multiple samples and the detection of a plurality of mutations or polymorphisms, thereby providing a faster, more efficient and economical method of prenatal diagnosis.

RESPONSE TO ARGUMENTS:

In the response, Applicants traverse this rejection by arguing that "the Fodor reference does not singularly disclose the novel features of claim 1." However, the present grounds of rejection were not applied under 35 USC 102 and there is no requirement for Fodor alone to teach each of the elements of claim 1. Rather, Fodor ws cited for its teachings of detecting a genetic anomaly or genotype using DNA probes fixed to a microarray.

5. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000), and further in view of Pinkel (U.S. Patent No. 6159685).

The teachings of Kalionis and Vona are presented above. In particular, Kalionis teaches prenatal diagnosis of fetal cells by in situ hybridization but does not teach using comparative genomic hybridization (CGH) for prenatal diagnosis.

However, Pinkel (paragraph 41) teaches the method of comparative genomic hybridization and teaches the application of this method to prenatal diagnosis by assaying nucleic acid sequences of fetal cells (see, e.g., paragraphs 8 and 14). Specifically, Pinkel (paragraphs 14 and 41) teaches that CGH employs the methodology of in situ hybridization in order to detect extra or missing copies of whole chromosomes or parts of chromosomes. Pinkel (paragraph 14) states: "(w)hen CGH is applied, for example, in the fields of tumor cytogenetics and prenatal diagnosis, it provides methods to determine whether there are abnormal copy numbers of nucleic acid sequences anywhere in the genome of a subject tumor cell or fetal cell or the genomes from representative cells from a tumor cell population or from a number of fetal cells, without having to prepare condensed chromosome spreads from those cells. Thus, cytogenetic abnormalities involving abnormal copy numbers of nucleic acid sequences, specifically amplifications and/or deletions, can be found by the methods of this invention in the format of an immediate overview of an entire genome or portions thereof. More specifically, CGH provides methods to compare and map the frequency of nucleic acid sequences from one or more subject genomes or portions thereof in relation to a reference genome. It permits the determination of the relative number of copies of nucleic acid sequences in one or more subject genomes (for example, those of tumor cells) as a function of the location of those sequences in a reference genome (for example, that of a normal human cell)."

In view of the teachings of Pinkel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of

Kalionis so as to have analyzed the isolated fetal cells by CGH in order to have provided a rapid and effective means for identifying genetic anomalies in the fetal nucleic acid, thereby facilitating the method of prenatal diagnosis.

RESPONSE TO ARGUMENTS:

In the response, Applicants traverse this rejection by arguing that Kalionis, Vona and Pinkel fail to disclose or suggest each element of claim 1, and thereby claim 18 is obvious over the combined references. However, for the reasons stated above, it is maintained that the combined references do in fact teach a method comprising each of the elements of claim 18.

The following are new grounds of rejection necessitated by Applicant's amendments to the claims:

6. Claims 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis and Vona, as presented above, and further in view of Bisconte (U.S. Patent No. 5,306,420).

The teachings of Kalionis and Vona are presented above. In particular, Kalionis (page 4) teaches filtering the blood through a filter that has a pore size of 10 um (i.e., a pore size "between 6 and 15 um"). Further, Vona teaches filtering blood through a "module of filtration (licenses EP513139, US5606351, JO5504405) kindly provided by the Biocom company (Les Ulis, France) and a polycarbonate Track-Etch-type membrane (Cyclotron Technology) with calibrated 8-um–diameter, cylindrical pores. The module of filtration has 12 wells, making it possible to load and filter 12 individual samples in parallel."

The combined references do not specifically teach that the blood is filtered through a device that comprises on a frame, a filter mounted between two filtering devices, a filtration seal, and a means for forced filtration, wherein the upstream clamping device provides a means for storing samples to be analyzed and the downstream clamping device comprises perforations for the storage means.

However, Bisconte (see, e.g., col. 6 and 7 and claim 1) discloses a method for filtering cells wherein the method requires the use of a filtration device comprising:

a porous filter that can retain cells based on size, wherein the filter is mounted between an upstream and a downstream clamping device;

a filtration seal (see, also column 8);

a means for storing or pre-treating samples which is upstream of the filter;

a perforated gasket facing a storage means which is downstream of the filter;

and a means for forced filtration (i.e., a pressure device or a suction device).

Bisconte (col. 2) teaches that the filtration device is advantageous because it allows for the filtering of multiple samples simultaneously, independently and in parallel. The filtering device also allows for cells deposited on the filter to be identified and monitored by a computer program. Also, the filtering device can be automated, with a computer being used to control the force of filtering (col. 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have used the filtration device of Bisconte because this would have provided an effective means for

storing, pre-treating and filtering multiple samples of maternal blood simultaneously, thereby providing an efficient and effective means for isolating and analyzing fetal cells.

With respect to claim 28, Vona teaches filtering blood to isolate epithelial cells through a membrane with a pore size of 8 um. Further, Bisconte ('420) teaches that the pore size of the filter is varied depending on the size of cell that is to be isolated (see col. 8). As discussed in MPEP2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Kalionis so as to have used a filtration device having a pore size of 8 um in order to have achieved the advantage of providing an effective method for isolating and collecting fetal cells present in maternal blood samples.

7. Claims 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis, Vona and Bisconte (U.S. Patent No. 5,306,420), as presented above, further in view of Bisconte (FR 2782730; cited in the IDS; note that the English translation of this document is US 2002/0028431; see page 1 of the FR 272730 document as filed).

The teachings of Kalionas, Vona and Bisconte are presented above.

With respect to claim 27, the combined references do not state the specific pressure that is applied to the filter in order to facilitate passage of fluids through the filter and retention of the target cells on the filter. However, Bisconte (FR 272730; page 4 and 5) teaches the use of a filtration device to isolate rare pathogenic cells, wherein

the filtration device has a partial vacuum of approximately 50,000 PA (i.e., 0.5 bars) under the filter. Further, the selection of an optimal filtration pressure based on the type and size of cell to be isolated was well within the skill of the art at the time the invention was made. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Kalionis so as to have used a filtration pressure of 50,000 PA in order to have accomplished the objective set forth by Bisconte (FR 272730) of providing an effective method for isolating and collecting rare pathogenic cells from blood samples in a manner sufficient to maintain the integrity of the cell and to have allowed for the isolation of individual cells.

With respect to claim 29, the combined references do not teach that the membrane has a pore density of 5×10^4 to 5×10^5 pores/cm^2. However, Bisconte (FR 272730) teaches that the filtration device is used to isolate and collect single cells. To have determined the optimum density of the pores that would allow for the isolation and collection of single cells from the filter membrane would have been obvious to one of ordinary skill in the art and well within the skill of the art. As discussed in MPEP2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In particular, Bisconte teaches the criticality of selecting a filter wherein the pore size is sufficient to retain the cell of interest and wherein the pores are spaced sufficiently a part to allow for the separation and isolation of individual cells. Accordingly, the

selection of a filter having an optimum pore density, including a pore density of 5×10^4 to 5×10^5 pores/cm^2 , would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made in order to have to have accomplished the objective of isolating and collecting the single pathogenic cells, thereby facilitating the method of diagnosis.

Response to arguments:

In the response, Applicants traversed the previous grounds of rejection over Bisconte ('420) in view of Bisconte ('730) by stating that the combined references do not teach filtering maternal blood to isolate fetal cells. However, in view of the amendment to the claims to recite a method for isolating fetal cells from maternal blood, the rejection has been modified as set forth above. In particular, Kalionis and Vona teach the filtering of maternal blood to isolate fetal cells and Bisconte is cited for its teachings of a filtering device to accomplish the objective of effectively and efficiently filtering cells present in a biological sample. As discussed above,ilt would have been obvious to one of ordinary skill in the art at the time the invention was made to have practiced the method of Kalionis in view of Vona using the filtration device of Bisconte in view of the advantages set forth by Bisconte that the filtering device provides an effective means for storing, pre-treating and filtering multiple samples simultaneously, thereby providing an efficient and effective means for isolating and analyzing fetal cells.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER